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HARRIET M. STRIMPEL, D. Phil. New England Biolabs, Inc. 240 COUNTY ROAD IPSWICH, MA 01938-2723				
EXAMINER RAMIREZ, DELIA M				
ART UNIT		PAPER NUMBER		
1652				
NOTIFICATION DATE		DELIVERY MODE		
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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### Office Action Summary

**Application No.**

10/593,790

**Applicant(s)**

MORGAN ET AL

**Examiner**

DELIA M. RAMIREZ

**Art Unit**

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 19 November 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 15 and 17-28 is/are pending in the application.
- 4a) Of the above claim(s) 23-28 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 15 and 17-22 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 September 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 9/25/06, 5/16/07.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Status of the Application***

Claims 15, 17-28 are pending.

Applicant's election of Group I, claims 15-22, drawn to a method of making a restriction endonuclease having altered specificity, as submitted in a communication filed on 11/19/2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant's amendment of claim 15 and cancellation of claim 16 as submitted in a communication filed on 11/19/2008.

Claims 22-28 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 15, 17-22 are at issue and are being examined herein.

### ***Specification***

1. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See, for example, page 2, line 21, page 14, line 5, page 41, line 8. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

### ***Priority***

2. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to provisional application No. 60/555,796 filed on 03/24/2004.
3. This application is the US national stage of PCT/US05/09824 filed on 03/23/2005.

***Information Disclosure Statement***

4. The information disclosure statements (IDS) submitted on 9/25/2006 and 5/16/2007 are acknowledged. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

***Drawings***

5. The drawings submitted on 9/25/2006 have been reviewed and are accepted by the Examiner for examination purposes.

***Claim Objections***

6. Claim 15 is objected to due to the recitation of "obtaining the restriction endonuclease". Since there is no antecedent basis for "the" restriction endonuclease with altered specificity, the term should be amended to recite "a restriction endonuclease with altered specificity". Appropriate correction is required.
7. Claim 20 is objected to due to the recitation of "specificity module" as there is no antecedent basis for a module. It is suggested the term be amended to recite "specificity subunit" to be consistent with previous claims.

***Claim Rejections - 35 USC § 112, Second Paragraph***

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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10. Claim 20 is indefinite in the recitation of "a method according to claim 15, 16..." in view of the fact that claim 16 has been canceled. For examination purposes, it will be assumed that there is no recitation of claim 16 in claim 20. Correction is required.

***Claim Rejections - 35 USC § 102***

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 15, 19-20, 22 are rejected under 35 U.S.C. 102(b) as being anticipated by MacWilliams et al. (The EMBL Journal 15(17):4775-4783, 1996; cited in the specification).

Claims 15, 19-20, 22 are directed in part to a method comprising the steps of (1) selecting a restriction endonuclease characterized by a modular structure wherein the endonuclease has a specificity subunit and a catalytic subunit, wherein the specificity subunit comprises an N-terminal domain which binds one half site of a bipartite recognition sequence and the C-terminal domain binds a second half of a bipartite recognition sequence, and (2) modifying the specificity subunit by mutating the N-terminal domain and/or the C-terminal domain as well as additional mutations to alter the length of the spacer between the N- and C-terminal domains to alter binding specificity, wherein the specificity subunit and the catalytic subunit are encoded by different genes.

MacWilliams et al. teach a method to generate a mutant restriction enzyme with a new DNA binding specificity, wherein the mutant restriction enzyme is obtained by deleting the N-terminal domain of the specificity subunit which recognizes the first half site of the sequence recognized by EcoDXXI as well as the TAEL repeats which are the spacer between the N- and C-terminal domains of the specificity subunit (page 4776, left column, last 9 lines-right column, first 6 lines; Figure 1). EcoDXXI is a type I

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restriction endonuclease and the specificity and catalytic subunits are encoded by the *hsdS* and the *hsdR/hsdM* genes, respectively (page 4775, right column, lines 4-8). MacWilliams et al found that the C-terminal domain of the specificity subunit can completely substitute for the missing N-terminal domain, and also disclose that a similar experiment where the C-terminal domain was deleted, showed that the N-terminal domain can completely substitute for the missing C-terminal domain (Abstract). Therefore, the teachings of MacWilliams et al. anticipate the instant claims as written.

13. Claims 15, 18-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Gubler et al. (The EMBL Journal 11(1):233-240, 1992).

Claims 15, 19-20, 22 are directed in part to a method comprising the steps of (1) selecting a restriction endonuclease characterized by a modular structure wherein the endonuclease has a specificity subunit and a catalytic subunit, wherein the specificity subunit comprises an N-terminal domain which binds one half site of a bipartite recognition sequence and the C-terminal domain binds a second half of a bipartite recognition sequence, and (2) modifying the specificity subunit by mutating the N-terminal domain and/or the C-terminal domain as well as additional mutations to alter the length of the spacer between the N- and C-terminal domains to alter binding specificity, wherein the specificity subunit and the catalytic subunit are encoded by different genes. Claims 18 and 21 are directed in part to the method of claim 15 as described above wherein the modification of the specificity subunit comprises substitution of either the N- or C-terminal domains with a second N- or C-terminal domain, wherein said second N- or C-terminal domain is that of a type I restriction endonuclease.

Gubler et al. teach a method of obtaining hybrid type I restriction endonucleases with altered DNA binding specificities wherein said hybrid type I restriction endonucleases are the result of exchanging the N-terminal or C-terminal domains of the specificity subunits of the EcoDXX1 and EcoR124I type I restriction endonucleases (Abstract, Figure 3B) as well as modifying the number of

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TAEL repeats (page 236, left column, lines 7-15-right column, lines 1-5) which are the spacer between the N- and C-terminal domains. As indicated above, type I restriction endonucleases have different genes encoding the specificity and catalytic subunits (hsdS, hsdR, and hsdM genes). Therefore, the teachings of Gubler et al. anticipate the instant claims as written.

***Claim Rejections - 35 USC § 103***

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over MacWilliams et al. (The EMBL Journal 15(17):4775-4783, 1996; cited in the specification) in view of Gubler et al. (The EMBL Journal 11(1):233-240, 1992). The teachings of MacWilliams et al. and Gubler et al. have been discussed above. MacWilliams et al. do not teach substituting the deleted N-terminal domain with the C-terminal domain of another restriction enzyme, or substituting the deleted C-terminal domain with the N-terminal domain of another restriction enzyme. Gubler et al. do not teach exchanging the N-terminal domain of the EcoDXXI restriction enzyme with the C-terminal domain of the EcoR1241 restriction

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enzymic, or vice versa, or the N-terminal domain of the EcoR124I restriction enzyme with the C-terminal domain of the EcoDXXI restriction enzyme, or vice versa.

Claim 17 is directed to the method of claim 15 as indicated above wherein the modifying step comprises substitution of the N-terminal domain with a second C-terminal domain or substitution of the C-terminal domain with a second N-terminal domain.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to further modify the mutant restriction endonucleases of MacWilliams et al. such that the deleted N-terminal domain was substituted with the C-terminal domain of a specificity subunit from another restriction endonuclease having the same type of structural configuration as that of a type I restriction enzyme with regard to the recognition site, or the deleted C-terminal domain was substituted with the N-terminal domain of a specificity subunit from another restriction endonuclease having the same type of structural configuration as that of a type I restriction enzyme with regard to the recognition site (i.e., bipartite recognition site where the N-terminus of the specificity subunit recognizes one part of the recognition site and the C-terminus of the specificity subunit recognizes the other part of the recognition site). A person of ordinary skill in the art is motivated to make those additional modifications to expand the range of recognition sites since the teachings of MacWilliams et al. and Gubler et al. clearly show that the presence of the domain that recognizes one half of the bipartite DNA binding site is not required to recognize the other half of the bipartite binding site, thus teaching that one could mix and match among N-terminal and C-terminal domains of specificity subunits to create new binding specificities. One of ordinary skill in the art has a reasonable expectation of success at making the recited modifications and alter the DNA binding specificity since (a) MacWilliams et al. teach that deletion of one terminal domain of the specificity subunit results in the recognition of a palindromic sequence, thus suggesting that (1) the mutant restriction endonucleases use two truncated specificity subunits for recognition (equivalent to two N-terminal domains linked together, or two C-terminal domains linked together), and (2) the remaining

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terminal domain can substitute for the missing terminal domain (page 4776, left column, lines 16-24; page 4779, right column, lines 2-13), and (b) Gubler et al. teach that one could obtain a hybrid restriction endonuclease with a different recognition site by exchanging the N- or C-terminal domains of different restriction enzymes which have a similar structural configuration and a bipartite binding site consisting of two parts, each recognized by the N-terminus or the C-terminus of the specificity subunit, respectively. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

### ***Conclusion***

17. No claim is in condition for allowance.

18. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez, Ph.D., whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 9:30:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashaat Nashed can be reached on (571) 272-0934. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Delia M. Ramirez/

Delia M. Ramirez  
Primary Patent Examiner  
Art Unit 1652

DR  
February 5, 2009